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No. 06-1642

IN THE

Supreme Court of the United States

TEVA PHARMACEUTICALS USA, INC. and
ZENITH GOLDLINE PHARMACEUTICALS
(now known as IVAX PHARMACEUTICALS, INC.),

Petitioners,

v.

ELI LILLY AND COMPANY and
LILLY INDUSTRIES LIMITED,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE
UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

REPLY BRIEF

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STATEMENT PURSUANT TO RULE 29.6

Petitioners' corporate disclosure statement was set forth at page *ii* of the Petition for a Writ of Certiorari, and there are no amendments to that statement.

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Petitioners Teva and Ivax (collectively "Teva") respectfully submit this reply brief in response to the opposition brief of Respondent Lilly and in support of Teva's petition for a writ of certiorari to vacate the judgment of the Federal Circuit and remand the case ("GVR") for reconsideration in light of *KSR Int'l Co. v. Teleflex Inc.*, No. 04-1350, 127 S. Ct. 1727 (2007).

REPLY ARGUMENT

I. The Federal Circuit Did Apply Three Rigid "Motivation" Requirements that Are Inconsistent with the Flexible Approach to Obviousness of *KSR*

Lilly argues that the Federal Circuit did not impose any of the three rigid "motivation" requirements identified by Teva as being inconsistent with the flexible approach to obviousness set forth by this Court in *KSR*. According to Lilly, the Federal Circuit simply considered and rejected Teva's arguments that olanzapine was obvious over ethyl olanzapine on their merits. Lilly Br. 13, 22-24. What Lilly overlooks is that the *reason* why the Federal Circuit rejected Teva's obviousness arguments was because they purportedly did not comply with these three rigid "motivation" requirements.

The Federal Circuit's opinion makes clear that it held that ethyl olanzapine should not be considered in evaluating the obviousness of olanzapine because purportedly there was no "motivation" to select ethyl olanzapine as a "lead compound." The court stated that "the defendants have not shown that a person ordinarily skilled in this art would have *selected* Compound '222 [ethyl olanzapine] as a *lead compound*" and that "rather than providing *the requisite*

motivation, the prior art taught away from *selecting* Compound '222 as a *lead compound* for further development." App. 16a (emphasis added).

Moreover, the Federal Circuit used the short-hand "nonobvious *selection* step" to describe this requirement and stated that "to establish a *prima facie* case of obviousness based on a combination of elements in the prior art, *the law requires a motivation to select the references* and to combine them in the particular claimed manner to reach the claimed invention." App. 18a (citations omitted) (second emphasis added).

Finally, if any doubt remained, the Federal Circuit cited as precedent its earlier holding in *Yamanouchi Pharm. v. Danbury Pharmacal* that "[[t]he ANDA filer] *did not show sufficient motivation* for one of ordinary skill in the art at the time of invention to take any one of the following steps . . . (1) *selecting* example 44 as a *lead compound*." App. 15a-16a (citing 231 F.3d 1339, 1344 (Fed. Cir. 2000) (emphasis added)).

It is also clear that the *reason* why the Federal Circuit held that there was no "motivation" to select ethyl olanzapine as a "lead compound" was because it was not described in the prior art as "preferred." The Federal Circuit endorsed the district court's finding that "a person of ordinary skill in the art would not have chosen Compound '222 as the beginning compound because it contained a hydrogen atom instead of a halogen atom, which again is *not a preferred substituent*." App. 14a (emphasis added).

Finally, the *reason* why the Federal Circuit held that there was no "motivation" to modify ethyl olanzapine to arrive at

olanzapine was because the proposed modification was not described in the prior art as "preferred." The court concluded that because the prior art "expressed *a preference* for halogen containing compounds" there was "no motivation" to modify ethyl olanzapine by substituting a methyl group because "[t]he prior art would have instead suggested modification by adding a halogen atom to supply the neuroleptic substituent as a trigger for antipsychotic activity." *Id.* at 14a-15a.

As Teva explained in its petition, each of these three rigid "motivation" requirements is inconsistent with the flexible approach to obviousness set forth in *KSR*. In short, both the district court and the Federal Circuit applied an incorrect legal framework in analyzing obviousness.

II. The Federal Circuit's "Lead Compound" Requirement Is Inconsistent with the Legal Framework for Analyzing Obviousness

Lilly also defends the Federal Circuit's rigid requirement that there has to be a "motivation" to select a prior art compound as a "lead compound" by asserting that "the evidence showed that in the pharmaceutical arts, selecting a lead compound was a standard part of the discovery of new drugs." Lilly Br. 15. Whether it is true or not, this sweeping *factual* assertion about pharmaceutical research is beside the point. The issue is whether the Federal Circuit applied the correct *legal* framework in analyzing obviousness. Its "lead compound" requirement—and Lilly's arguments in defense of that requirement—find no support in, and are inconsistent with, Section 103 of the patent statute and precedent.

In cases such as this one that involve the obviousness of structurally similar chemical compounds, there has never

been a requirement—prior to the Federal Circuit's decision in this case—that there must be a "motivation" to select the structurally closest prior art compound as a "lead compound." To the contrary, the legal framework for analyzing obviousness in such cases takes as its starting point the prior art compound that is structurally closest to the claimed compound and then analyzes whether it would have been obvious to make the claimed compound.

In an earlier *en banc* decision, the Federal Circuit held that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness." *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc). The court explained that a "presumption of obviousness or a *prima facie* case of obviousness" arises when a prior art compound is "close enough to the claimed invention to give one skilled in the relevant chemical art the motivation to make close relatives (homologs, analogs, isomers, etc.) of the prior art compound(s)." *Id.* at 696.

Unlike the "lead compound" requirement, the approach set forth in *Dillon* is consistent with Section 103 and this Court's precedent, both of which require one to determine whether the claimed subject matter would have been obvious after *comparing and ascertaining the differences* between the claim and the prior art. 35 U.S.C. § 103(a); *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966) ("Under § 103, the scope and content of the prior art are to be determined; *differences between the prior art and the claims at issue are to be ascertained*; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined." (emphasis added)).

In short, the legal framework for analyzing obviousness in a case that involves structurally similar chemical compounds takes as its starting point the structurally closest prior art compound. The Federal Circuit's additional requirement in this case that there has to be a "motivation" to select this structurally closest prior art compound as a "lead compound" finds no support in, and is inconsistent with, this legal framework. Accordingly, contrary to Lilly's argument, it was not "impermissible hindsight" to start with ethyl olanzapine based on its "structural similarity to olanzapine." Lilly Br. 14, 18-19.[1] To the contrary, in a case such as this one that involves an adjacent homolog, the law requires one to start from this very point.[2]

Finally, Lilly's reliance on two other decisions in which the Federal Circuit endorsed the "lead compound" requirement is misplaced. Lilly Br. 16 (citing *Yamanouchi*,

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1. Lilly relies on this Court's statements in *KSR* warning against "the distortion caused by hindsight bias" and being "cautious of arguments reliant upon *ex post* reasoning." Lilly Br. 14, 19 (quoting 127 S. Ct. at 1742). But it is clear from the context of those statements that this Court was responding to the Federal Circuit's explanation that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to *combine* prior art references." *Teleflex, Inc. v. KSR Int'l*, 119 Fed. Appx. 282, 285, No. 04-1152, 2005 U.S. App. LEXIS 176, *8 (Fed. Cir. Jan. 6, 2005) (citation omitted) (emphasis added). In other words, this Court did not hold that there must be a "motivation" to select prior art to guard against hindsight, and it certainly did not endorse any requirement that there must be a "motivation" to select a "lead compound" in a chemical case.

2. Indeed, during the prosecution of the '382 patent, the examiner rejected claims to olanzapine as obvious over ethyl olanzapine without considering whether there was a "motivation" to select ethyl olanzapine as a "lead compound." C.A. App. A398-99.

231 F.3d at 1344; *Takeda Chem. Indus. v. Alphapharm Pty.*, 492 F.3d 1350 (Fed. Cir. 2007)).

Yamanouchi pre-dates *KSR* by several years and is replete with references to the "motivation" requirement that this Court criticized in *KSR*. *See, e.g.*, *Yamanouchi*, 231 F.3d at 1343-46. Moreover, unlike this case, *Yamanouchi* did not involve two almost structurally identical compounds. The complicated issue in that case was "whether one of skill in this art would have found motivation to combine pieces from one compound in a prior art patent with a piece of another compound in the second prior art patent *through a series of manipulations*." *Id.* at 1343 (emphasis added). The district court found that it would not have been obvious "to take the *myriad components of various teachings of prior art* and combine them." *Yamanouchi Pharm. v. Danbury Pharmacal*, 21 F. Supp. 2d 366, 372 (S.D.N.Y. 1998) (emphasis added). The phrase "lead compound" does not appear in the district court opinion at all.

On appeal, the defendants in *Yamanouchi* argued that there would have been a motivation to modify the prior art "compound 44" because it was known to be a "lead compound." Thus, the issue of whether that prior art compound was a "lead compound" was raised by *defendants* as a means of supporting their own "motivation or suggestion" argument. *See Yamanouchi*, 231 F.3d at 1343-44 ("*According to Danbury*, one of skill in the art would have considered it obvious to *select* the example 44 compound . . . and tiotidine from the '378 patent *to use as leads* for making famotidine." (emphasis added)). The Federal Circuit responded to defendants' argument by finding that they had not proven their *own* assertion that compound 44 was a "lead compound." *Id.* at 1345. That the identification

of a "lead compound" may be *one way* to prove the obviousness of a claimed compound, as defendants attempted to do in *Yamanouchi*, does not lead to the general rule that it is the *only way* to do so, which is what the Federal Circuit held in this case.

A similar scenario presented itself in *Takeda*. Once again, as part of their obviousness case the *defendants*, for their own reasons, assumed the burden of proving that there was a "motivation" to select a prior art compound known as "compound b" as a "lead compound." *See Takeda*, 492 F.3d at 1356-57 ("*Alphapharm's* obviousness argument clearly *depends* on a preliminary finding that one of ordinary skill in the art would have *selected* compound b as a *lead compound*." (emphasis added)); *see also id.* n.3 ("We will, however, *use Alphapharm's terminology of "lead compound"* in this opinion, deciding the appeal *as it has been argued*." (emphasis added)). That manifestly is *not* the case here, where Lilly—not Teva—injected the "lead compound" requirement into the case. Moreover, although *Takeda* came down after *KSR*, the only authority that the *Takeda* court cited for the "lead compound" requirement is, perhaps not surprisingly, the Federal Circuit's decision *in this case*, which, of course, was incorrectly decided. *Id.* at 1360 (citing *Eli Lilly & Co. v. Zenith Goldline Pharms.*, 471 F.3d 1369 (Fed. Cir. 2006)).

III. The Prior Art Did Not "Teach Away" from Non-Halogenated Compounds Such As Ethyl Olanzapine Even If They Purportedly Were Described As Not "Preferred"

Lilly also repeatedly argues that the prior art "taught away" from selecting and modifying ethyl olanzapine to arrive at olanzapine. According to Lilly, the preference in the prior art for halogenated compounds that have a neuroleptic substituent "taught away" from selecting a non-halogenated compound such as ethyl olanzapine and from modifying it to create another non-halogenated compound. Lilly Br. 8-9, 21-24 (citing *United States v. Adams*, 383 U.S. 39, 52 (1966)).

Lilly's "teaching away" argument is flawed for two reasons. First, it is based in part on the premise that there has to be a "motivation" to select a "lead compound," which, as explained above, is incorrect. Second, the argument misapplies the law regarding when the prior art "teaches away."

Under this Court's precedent, the prior art *may* "teach away" when it would have "discouraged" or "deterred" one of ordinary skill in the art from pursuing the patented solution. *See Adams*, 383 U.S. at 52 ("These long-accepted factors, when taken together, would, we believe, *deter any investigation* into such a combination as is used by Adams . . . . known disadvantages in old devices which would *naturally discourage the search* for new inventions *may* be taken into account in determining obviousness." (emphasis added)).

The Federal Circuit applied this precedent in *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) ("A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be *discouraged* from following the path set out in the reference, or would be led in a direction *divergent* from the path that was taken by the applicant." (emphasis added) (citing *Adams*, 383 U.S. at 52; other citations omitted)). In that case, the patent application claimed an epoxy-based circuit board; the prior art taught that epoxy-based circuit boards are "inferior" to resin-based circuit boards. *Id.* at 552-53. The court found that the statement of inferiority in the prior art did not teach away from the claimed invention, and held that "[a] known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *Id.* at 553.

Likewise, the prior art does not "teach away" when it merely suggests that other options are "preferred" or more "desirable":

> [O]ur case law does not require that a particular combination must be the *preferred*, or the *most desirable*, combination described in the prior art in order to provide motivation for the current invention. . . . [t]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not *criticize*, *discredit*, or otherwise *discourage* the solution claimed.

In re Fulton, 391 F.3d 1195, 1200-01 (Fed. Cir. 2004) (emphasis added); *see also Merck & Co. v. Biocraft Labs.*, 874 F.2d 804, 807 (Fed. Cir. 1989) ("the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including *unpreferred* embodiments, must be considered." (emphasis added) (citation omitted)).

Therefore, contrary to Lilly's argument, even if the prior art expressed a preference for halogenated compounds, it did not "teach away" because the prior art did not "criticize" or "discredit" the use of ethyl olanzapine, and would not have "discouraged" or "deterred" one of ordinary skill from selecting or modifying ethyl olanzapine. Ethyl olanzapine is the next adjacent homolog of olanzapine and could not be structurally closer to olanzapine. It also is the first among the approximately 100 compounds (out of a genus of over one million) specifically identified in the prior art '574 patent as having anti-psychotic properties. App. 8a, 15a, *id.* at 66a-67a, ¶¶ 128-34. The fact that the '574 patent also expresses a preference for halogenated compounds does not undermine this separate teaching about ethyl olanzapine's utility. Moreover, the Chakrabarti 1980a article taught the desirability of substituting a short alkyl group (such as an ethyl group or a methyl group) because that increased the central nervous system activity. App. 68a-69a, ¶¶ 136-39; C.A. App. A22701-02. The fact that the Chakrabarti 1980a article made this statement in the context of the preferred halogenated compounds does not "teach away" from making the same modification in non-halogenated compounds like ethyl olanzapine.

CONCLUSION

For the foregoing reasons, and for the reasons set forth in the petition for certiorari, Petitioners Teva and Ivax respectfully request that this Court grant the petition, vacate the judgment, and remand the case to the Federal Circuit ("GVR") for reconsideration in light of *KSR Int'l Co. v. Teleflex Inc.*, No. 04-1350, 127 S. Ct. 1727 (2007).

Respectfully submitted,

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